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# **Supplementary Online Material: Bootstrap Enhanced Penalized Regression for Variable Selection with Neuroimaging Data**

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## **1 MULTIVARIATE FUNCTIONAL CONNECTIVITY ANALYSIS**

Multivariate methods for the analysis of fMRI data have become a popular alternative to univariate or bivariate techniques as they are designed to yield statistically optimal summaries of large quantities of data (Cox and Savoy, 2003). Multivariate approaches are particularly pertinent to functional connectivity studies that aim to characterize the communication of regions across the brain (Van De Ven et al., 2004). Historically, functional connectivity studies relied on seed based methods, where the average time series of one voxel cluster (the seed) was correlated with the time series from voxel clusters in other brain regions (Biswal et al., 1995; Lowe et al., 1998). Previous literature has identified at least two potential biases associated with seed-based techniques.

First, seed based techniques are biased by the strategies used to select the seed region and its theorized correlates. The brain does not contain a single hub with projections throughout the cortex. Instead, the brain is composed of numerous spatially distributed and functionally related regions (or networks) that each have multiple hubs (Bullmore and Sporns, 2012; Tomasi and Volkow, 2011; Van den Heuvel and Pol, 2010). Second, different types of fMRI noise, such as variance associated with physiological artifacts (e.g., head motion, cardiac function), can introduce bias into subsequent analyses (Beckmann et al., 2005; Liu et al., 2012; Van De Ven et al., 2004). A simple bivariate statistic, such as a correlation, cannot account for variance associated with physiological artifacts (Beckmann et al., 2005). Multivariate methods are more suitable in this context as they potentially control for such variables.

An increasingly used multivariate alternative to traditional univariate approaches is the application of ICA to fMRI data (Beckmann and Smith, 2004; Jafri et al., 2008). Briefly, ICA is a “temporal model-free” method that uses blind source separation to identify the underlying multivariate signals and structured noise in the data (De Luca et al., 2006; Smith et al., 2004). ICA accomplishes this decomposition without the use of a temporal model (Beckmann and Smith, 2004; Beckmann et al., 2005) or assumptions about the underlying biology (Esposito et al., 2005; Ramnani et al., 2004). Thus, ICA is a powerful data-driven approach for evaluating natural functional connectivity (Calhoun et al., 2009).

In the context of fMRI, ICA decomposes 4-dimensional data (3 spatial, 1 time) into spatial maps and their corresponding time courses. Components derived from fMRI data have been referred to as intrinsic connectivity networks (ICNs) as they are believed to reflect the brain’s inherent architecture both at rest and during task completion (Laird et al., 2011; Smith et al., 2009). One strength of this methodology is its capacity to reduce signals from millions of voxels into a set of functionally interpretable components

(Duff et al., 2012). However, many researchers are interested in how the strengths (or weaknesses) of ICNs underlie psychopathology (Bressler and Menon, 2010; Calhoun and Adali, 2012).

The ICA process itself cannot tell us which networks are important to one or more criteria of interest. For instance, researchers may be interested in whether spatial or temporal characteristics of the independent networks predict self-report measures (Wisner et al., 2013b), task-related BOLD activation (Mennes et al., 2010; Moodie et al., 2014), or group differences (Calhoun et al., 2012). Thus, additional methods are needed to identify the subset of substantively important networks. Ordinary least squares (OLS) regression models have often been used for this purpose (Choi et al., 2013; Eaton et al., 2012; Kim et al., 2009; Mennes et al., 2010; Stevens et al., 2007); however, as we explain in the manuscript, OLS regression may be ill-suited for this task.

## 2 THE NEURAL BASIS OF EXTERNALIZING

The externalizing spectrum includes a range of traits and behaviors, such as impulsivity, aggression, and substance use (Krueger et al., 2007). These traits have been shown to occur along a continuum from clinical to non-clinical populations. Moreover, externalizing problems can produce substantial psychological and functional ramifications, which in turn, engender significant financial costs to the community (Woltering et al., 2011). As such, researchers seek to elucidate the neural mechanisms that underlie externalizing behaviors and related psychopathology. A breadth of literature has linked the prefrontal cortex and ventral striatum with externalizing (Crews and Boettiger, 2009). More recently, several researchers have demonstrated the importance of the insula in externalizing psychopathology (Carroll et al., 2015; Goldstein et al., 2009; Naqvi and Bechara, 2009; Wisner et al., 2013b; Xue et al., 2010). This burgeoning research linking the insula with externalizing serves as the basis for our analyses. In this paper, we present findings that relate insula connectivity with externalizing traits in a non-clinical sample.

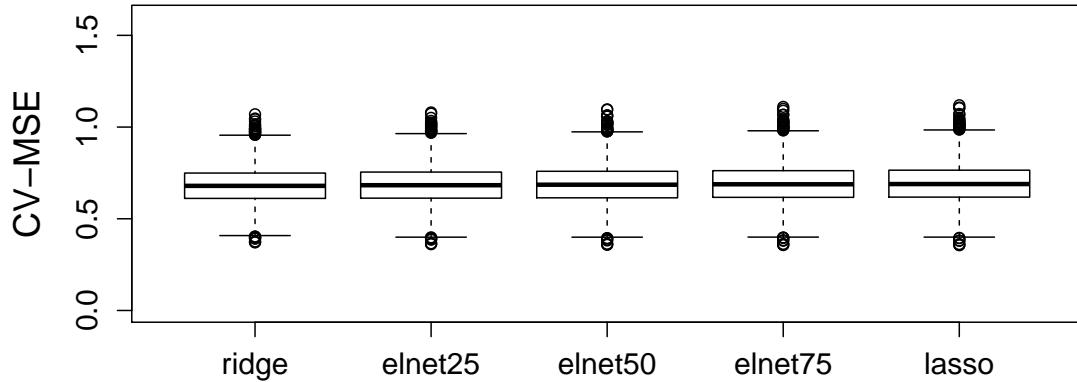
## 3 APPLYING ICA TO RESTING FMRI DATA

The full sample of data includes an additional 122 female subjects that were not included in the penalized regression analyses presented in the paper.<sup>1</sup> ICNs were generated using a meta-ICA procedure that was designed to optimize network reliability using the full sample of 244 participants (Moodie et al., 2014; Poppe et al., 2013; Wisner et al., 2013a). This procedure entailed running 25 temporal concatenation (model-free and multi-subject) group-level probabilistic ICAs. Each lower-level ICA included a random subject order of 80 participants as inputs (sampled from the 244), and was constrained to a dimensionality of 60, due to computational/hardware limitations and to reduce chances of over-fitting. The resulting 60 components from each lower-level ICA were then concatenated into a single file ( $60 \times 25 = 1500$  components total). The concatenated file was then employed as the input to a single meta-level MELODIC (hence, meta-ICA) to derive the 60 most consistent group-level components. Our choices to include 25 random subject orders with a dimensionality constraint of 60 were based on reliability analyses detailed by Poppe et al. (2013).

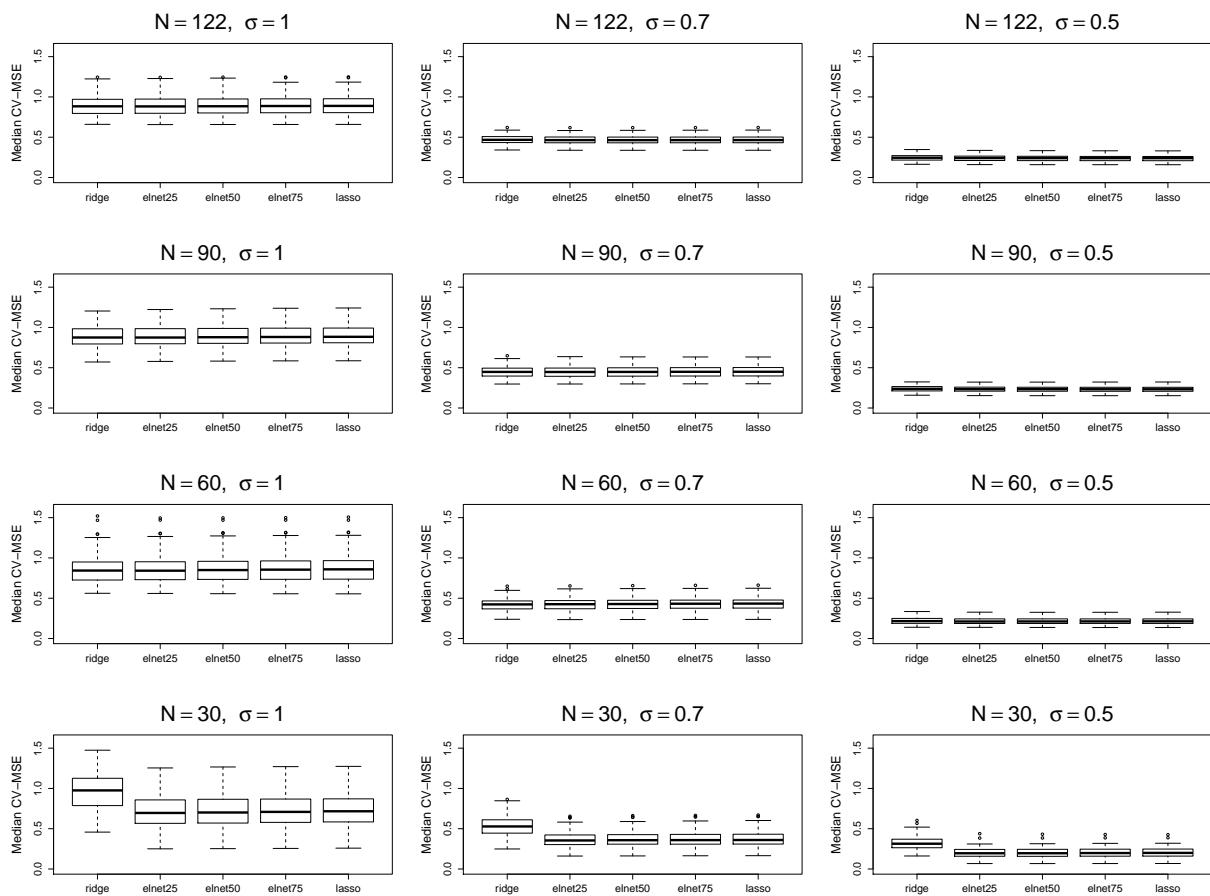
## 4 SUPPLEMENTARY FIGURES

<sup>1</sup> We included only males in our demonstration given notable sex differences in externalizing psychopathology (Eaton et al., 2012; Kramer et al., 2008; NolenHoeksema, 2004) and insula morphology and function (Lee et al., 2009; Moriguchi et al., 2014; Stevens and Hamann, 2012; Tanabe et al., 2013).

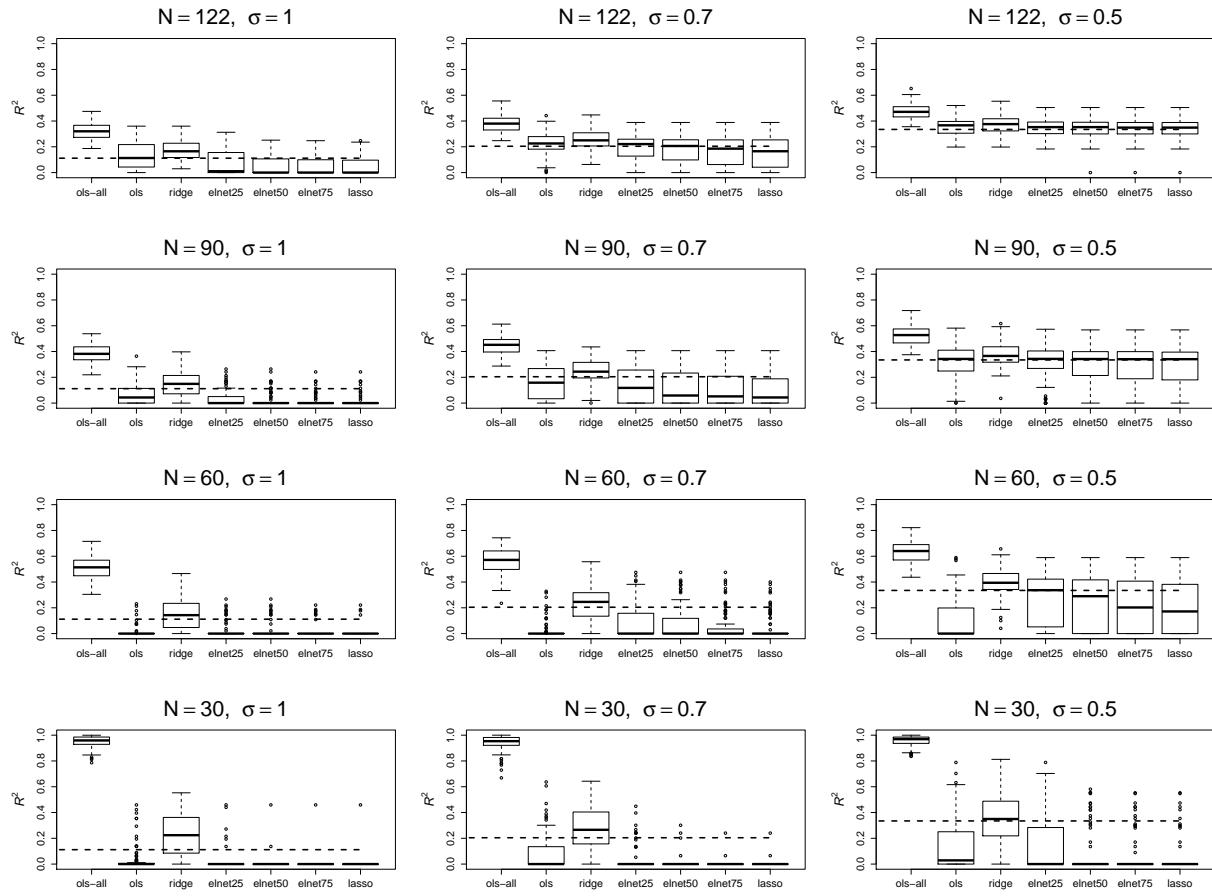
## Bootstrap Results: Real Data



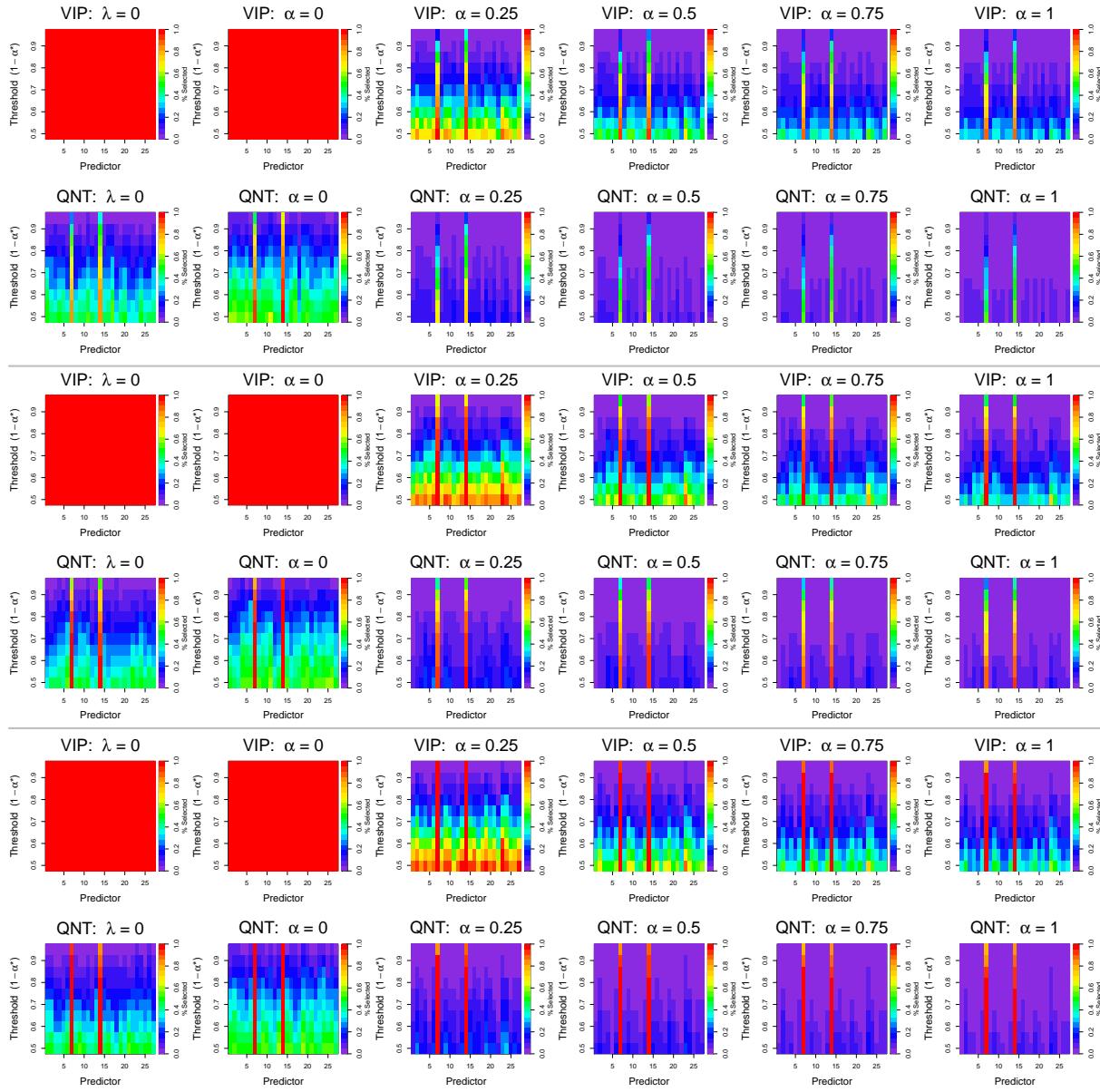
**Figure S1.** Visualization of bootstrapped model fit (cross-validated mean-squared error, or CV-MSE) for real data across penalized regression methods.



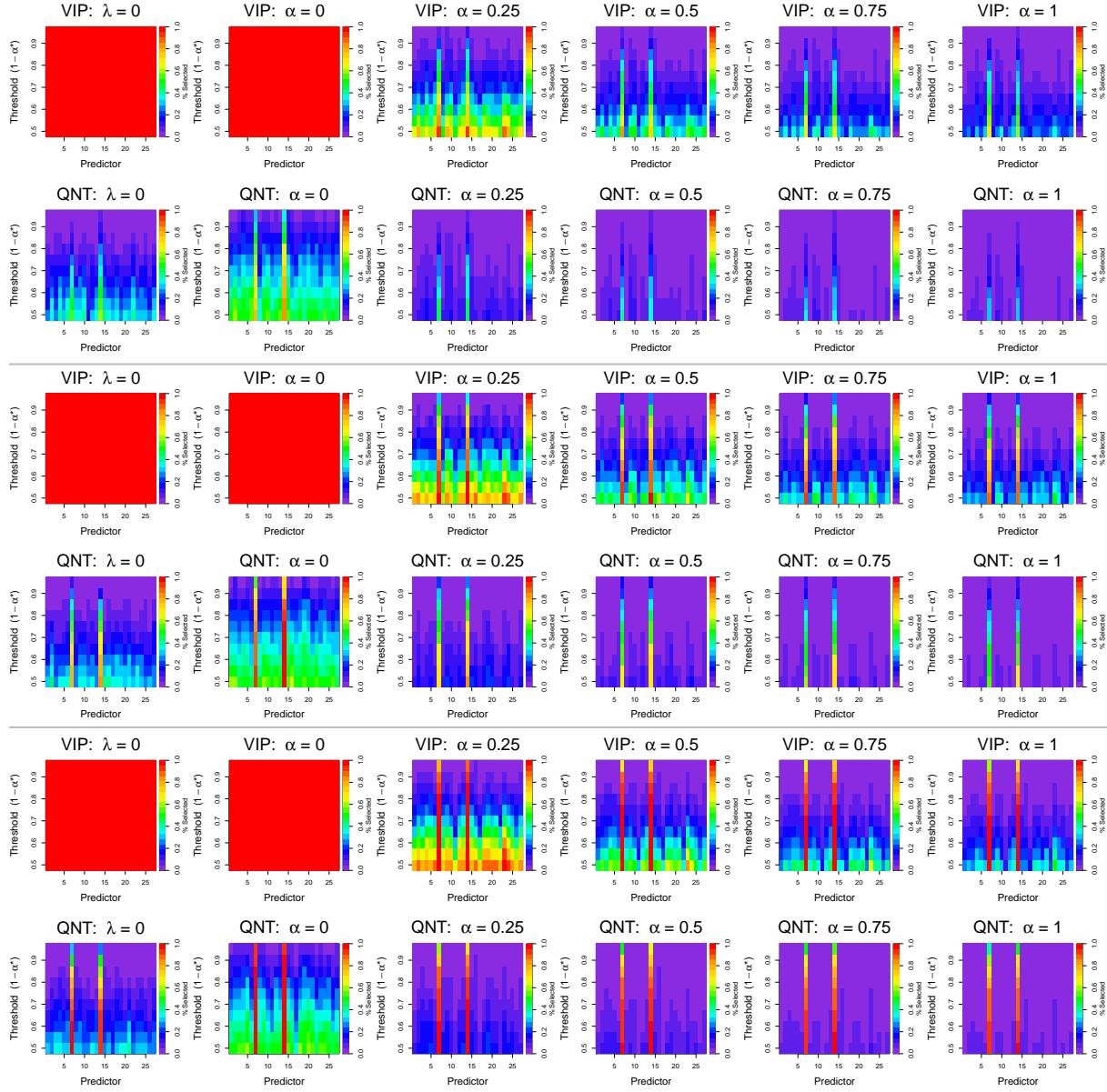
**Figure S2.** Illustrations of model fit (cross-validated mean-squared error or CV-MSE) across different sample sizes and signal-to-noise ratios for OLS regression when the model includes all possible predictors (ols-all), OLS regression (ols), ridge regression (ridge), elastic net where  $\alpha = 0.25$  (elnet25), elastic net where  $\alpha = 0.5$  (elnet50), elastic net where  $\alpha = 0.75$  (elnet75), and the lasso (lasso).



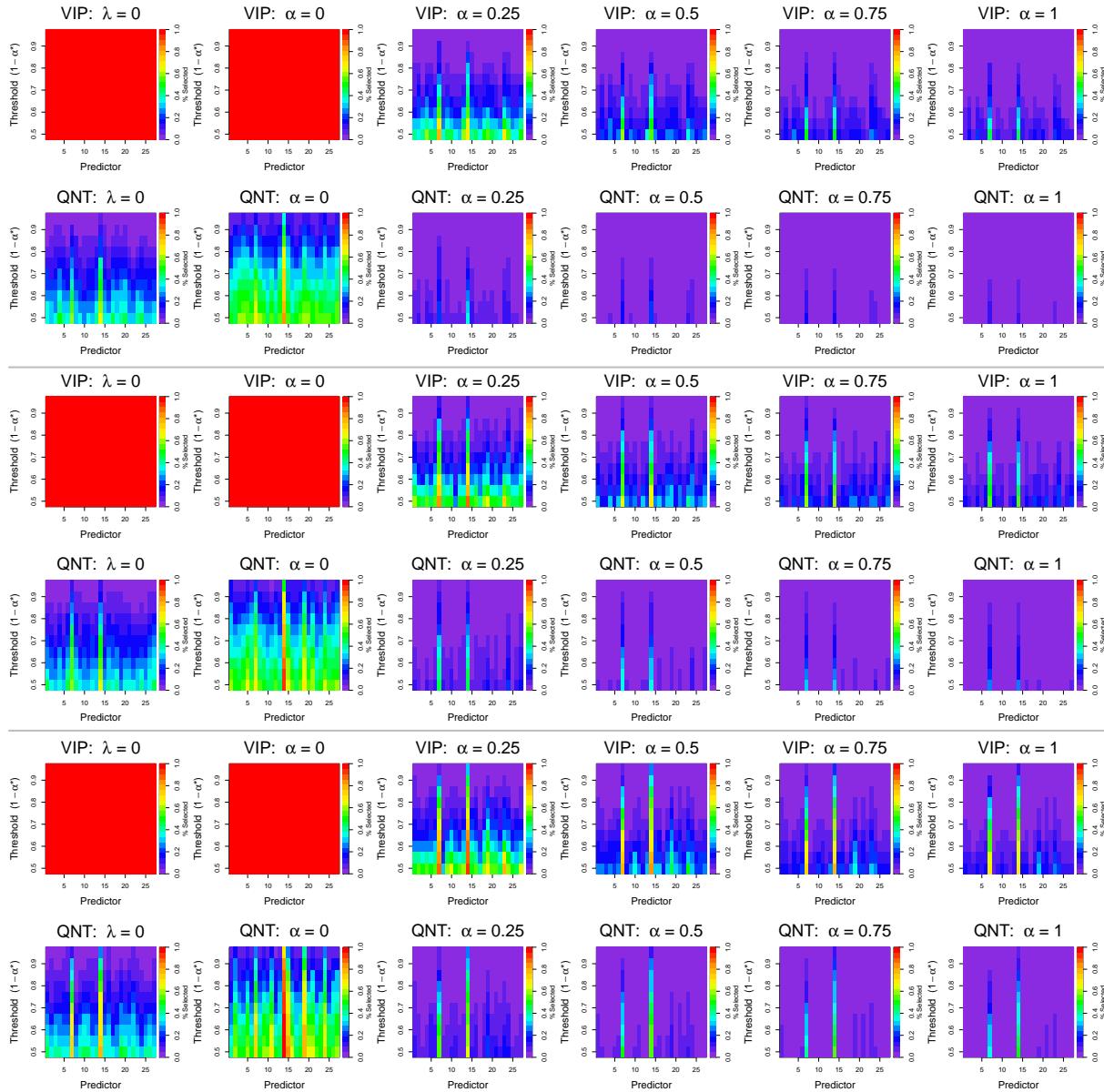
**Figure S3.** Illustrations of model fit ( $R^2$ ) across different sample sizes and signal-to-noise ratios for OLS regression when the model includes all possible predictors (ols-all), OLS regression (ols), ridge regression (ridge), elastic net where  $\alpha = 0.25$  (elnet25), elastic net where  $\alpha = 0.5$  (elnet50), elastic net where  $\alpha = 0.75$  (elnet75), and the lasso (lasso).



**Figure S4.** Results from simulated data analyses with  $n = 90$  subjects using the VIP approach (top) and the QNT approach (bottom). The top two rows display results for a signal-to-noise ratio (SNR) of 1, the middle two rows for a SNR of 0.7, and the bottom two rows for a SNR of 0.5. Each column represents a different regression model: OLS ( $\lambda = 0$ ), ridge regression ( $\alpha = 0$ ), elastic net ( $\alpha = 0.25, 0.5, 0.75$ ), and the lasso ( $\alpha = 1$ ). Colored bars indicate how often a specific predictor, i.e., network derived using ICA, was selected at a given significance threshold; the color scale represents the percentage of times that a predictor was selected across 100 simulation replications.



**Figure S5.** Results from simulated data analyses with  $n = 60$  subjects using the VIP approach (top) and the QNT approach (bottom). The top two rows display results for a signal-to-noise ratio (SNR) of 1, the middle two rows for a SNR of 0.7, and the bottom two rows for a SNR of 0.5. Each column represents a different regression model: OLS ( $\lambda = 0$ ), ridge regression ( $\alpha = 0$ ), elastic net ( $\alpha = 0.25, 0.5, 0.75$ ), and the lasso ( $\alpha = 1$ ). Colored bars indicate how often a specific predictor, i.e., network derived using ICA, was selected at a given significance threshold; the color scale represents the percentage of times that a predictor was selected across 100 simulation replications.



**Figure S6.** Results from simulated data analyses with  $n = 30$  subjects using the VIP approach (top) and the QNT approach (bottom). The top two rows display results for a signal-to-noise ratio (SNR) of 1, the middle two rows for a SNR of 0.7, and the bottom two rows for a SNR of 0.5. Each column represents a different regression model: OLS ( $\lambda = 0$ ), ridge regression ( $\alpha = 0$ ), elastic net ( $\alpha = 0.25, 0.5, 0.75$ ), and the lasso ( $\alpha = 1$ ). Colored bars indicate how often a specific predictor, i.e., network derived using ICA, was selected at a given significance threshold; the color scale represents the percentage of times that a predictor was selected across 100 simulation replications.

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